REMARKS

By this amendment claims 1, 3 and 4 are amended; claims 1-8 are pending. Support for the claim amendments is found in the specification as filed, for example, in the original claims and at page 4, lines 4 and 5, and the last full sentence. No issue of new matter arises. Entry of the amendment and reconsideration and withdrawal of all pending rejections in each of the multiple parts thereof are respectfully requested.

Applicants respectfully request withdrawal of finality of the present Office Action. Applicant was not permitted to properly respond to a previous rejection that on its face referred to Parkinson's disease, but in this Office Action has been modified to apply to Alzheimer's disease. This change cannot properly said to have been necessitated by Applicants' amendment. Thus withdrawal of finality is deemed proper. Entry of claim amendments therefore remains a matter of right.

Rejection Under 35 USC §101

Claims 1-8 were rejected under 35 USC §101 as allegedly lacking patentable utility. Applicants respectfully traverse this rejection.

The Office Action acknowledged that the transgenic animal model could be used to monitor apoptosis. However, the Office Action then asserted that "correlation or relationship to human disorder is not readily apparent." Then the Office Action continued its reasoning with: "A description of what a material does, rather than of what it is, usually does not suffice."

Applicants respectfully submit that this rejection is clearly improper. The present invention relates to a transgenic animal "expressing a multimutated form of presenilin 1". What the invention is is clearly recited. What the invention is capable of (or does) is also recited in the same independent claim. However, since "what it is" is clearly recited in the claim, the citation of *Reagents of Univ. of Cal. V. Eli Lilly & Co., Inc.* is improper support for the rejection. For at least his reason reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

Another assertion made by the Office Action related to a relationship between mutant PS1, apoptosis and Alzheimer's disease. The Office Action asserted that mice described in the specification would need further characterization. Applicants believe that this aspect of the

rejection is improper. Applicants respectfully submit that the claims do not recite Alzheimer's disease and thus assertions relating specifically to Alzheimer's disease are not understood. Alzheimer's disease is but one disease known to involve an altered apoptotic etiology. A real world association between the multi-mutated gene and monitoring apoptosis has been shown. Apoptosis is known to be a process important for growth and maintenance of animals. Malfunction of apoptotic pathways has been observed in many disease states, including neurodegenerative diseases. Thus a "real world" utility for the instant invention is apparent. Reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

The Office Action further acknowledged the showing in the specification that the animals of the instant invention exhibit increased sensitivity to apoptosis such as found in Alzheimer's disease. Applicants respectfully submit that this showing provides ample evidence of "real world" utility. However, the Office Action chose one indication of Alzheimer's disease, amyloid plaques, and asserts that since animals were not sacrificed for the express purpose of observing plaques, that a relationship between Alzheimer's disease and the mutant PS1s was unclear. Applicants respectfully submit that this is an improper standard. It is improper for the Office to require that all possible manifestations of a disease state be proven in a model to show utility in monitoring a disease state. Applicants respectfully illustrate the fallacy of this requirement by noting that human Alzheimer's disease patients are frequently diagnosed without invasion biopsy of their brain tissue, followed possibly with with confirmation of the disease only coming in selected individuals *post mortem*. Plainly Alzheimer's disease can be monitored without requirement to sample plaques along the way.

In view of the above comments, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §101 utility rejection.

Rejections Under 35 U.S.C. §112

Claims 1-8 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection. This rejection is constructed in several aspects or parts. To provide a complete response the recognized parts are addressed in turn below.

Applicants gratefully acknowledge the clarification by the Examiner that the basis of the rejection is not related to genetic mutations associated with apoptosis, but rather the enablement

rejection relates to a biological relationship between apoptosis, Alzheimer's disease and mutant PS1. In their traversal Applicants respectfully quote from the specification, page 6, paragraph 2:

> Thus, the results described in the examples demonstrate that the transgenic mouse expressing the multimutated PS1 develops cellular impairments which are found in Alzheimer's disease and, in particular, exhibits increased sensitivity to apoptosis.

Applicants respectfully submit that a biological relationship between the recited mutations and the recited capabilities is shown in the specification. Reconsideration and withdrawal of this rejection are respectfully requested.

Regarding promoters the Office Action asserts that insect embodiments might not be enabled. To expedite prosecution, claim 1 is amended to recite "mammalian". Support can be found in the specification as filed, for example, at page 4, lines 4 and 5. No issue of new matter arises. Applicants reserve the prerogative to seek broader claim scope in one or more continuation applications. This aspect of the rejection is thereby obviated. Reconsideration and withdrawal of this rejection are respectfully requested.

Another aspect of the rejection seems to involve speculation that rather than a mutated gene having effect, the effect may be due to inactivation of a gene at an insertion site or that some unforeseen unpredictable event might mitigate operation of the transgenic model. See page 7, top paragraph. Applicants respectfully submit that experience has shown that the transgenic model is repeatable. Applicants respectfully refer to the specification, e.g., at page 3, line 12, where multiple examples of successful transgenic production are described. Thus the transgenic process is in this respect repeatable and no undue experimentation would be required to make or use the claimed invention.

Another aspect of the rejection related to renewable tissue. Applicants again respectfully assert that inoperative embodiments are permitted. Thus comments relating, for example, to red blood cells that cannot apoptose are still valid. The present Office Action asserted that no guidance was provided for observing apoptosis in other tissues such as renewable peripheral tissues. Applicants respectfully submit that such guidance is unnecessary since methods for observing apoptosis in a variety of tissues are known in the art. The enablement requirement is not to be interpreted in a vacuum, but the skill of the art is expected to be employed by the skilled artisan wishing to practice the claimed invention. Thus the comment relating to guidance

not being found in the specification is not a proper standard for maintaining this aspect of the enablement rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

With respect to the aspect of the rejection expressed in the paragraph bridging pages 8 and 9, Applicants respectfully refer to the specification at page 6 to counter the assertion in the Office Action:

> Thus, the results described in the examples demonstrate that the transgenic mouse expressing the multimutated PS1 develops cellular impairments which are found in Alzheimer's disease and, in particular, exhibits increased sensitivity to apoptosis. This phenomena is moreover not observed with a simple pathological mutant of the M146L type. This phenotype is specifically obtained with a nonnatural form grouping together several individual mutations, and preferably 5 mutations, on the same cDNA. In addition, through the ectopic expression of the transgene by virtue of the ubiquitous promoter, this model makes it possible to detect an apoptotic phenomenon (linked to the mutations in Alzheimer's disease) in a renewable peripheral tissue. This model therefore provides a much more practical source of material (not requiring sacrificing the animal), therefore allowing longitudinal monitoring.

The specification is replete with associations between the model and Alzheimer's disease. See, *inter alia*, page 7, second paragraph. The assertion made in the Office Action that "nothing in the specification teaches a biological relationship between mutations in PS1 and apoptotic T lymphocytes that an artisan would know that there is a distinct phenotype caused by the presence of mutant PS1 in the cell." is plainly without proper support. Accordingly, reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

In a separate rejection commencing on page 10, claims 1-8 were rejected 35 U.S.C. §112, first paragraph, as allegedly lacking written. Applicants respectfully traverse this rejection.

The response in the Office Action was that every hybridization does not result in finding a homolog. The Office Action further asserted that "nothing in the art or specification provide example (structural/functional guidance) . . ." Applicants respectfully submit that homologous genes are known in the art to have similar structural features. Thus knowledge of on member of a gene family provides guidance of the structure of other members. With respect to mutations, structural similarity allows comparison between homologous genes. In some cases corresponding amino acids may be identically numbered; in other cases (where there are deletions or inserts) not. Sequence comparison, including gaps and insertions, is well known in

the art. Amino acids in one homolog corresponding to amino acids in other members of the family are readily identifiable. The assertion relating to "nothing" in the Office Action is plainly in error. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

In the Office Action at page 12, claim 4 was again rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite. While Applicants do not agree that the allegation of indefiniteness was proper, as offered in the previous reply, claim 4 is amended to recite claimed subject matter in a *Markush* format.

Conclusion

The foregoing is submitted as a full and complete response to the Action mailed on April 4, 2006, and the allowance of all claims is respectfully requested. If there are any issues that can be resolved by a telephone conference or an Examiner's amendment, the Examiner is invited to call the undersigned attorney at (908) 231-3776.

Applicants reiterate the previous request to withdraw finality of this Office Action. Applicants should not be penalized for the Office's typographical errors. See the Office Action, page 8, 4 lines from the bottom. Accordingly entry of this amendment is deemed proper.

Alternatively, if finality is maintained, entry of the amendments is proper under 37 C.F.R. §1.116 because the claim amendments i) place the application in condition for allowance; ii) do not raise new issues requiring further search and/or consideration; iii) comply with a suggestion made in the Office Action; and/or place the application in better condition for appeal should an appeal be necessary.

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt issuance of a Notice of Allowance. Should the Examiner wish to suggest additional changes that might put the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized to charge the fee required and any additional fees that may be needed to Deposit Account No. 18-1982.

Respectfully submitted,

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